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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
BAKER, A	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary	Application No. 09/289,576	Applicant(s) ALLEN ET AL.	
	Examin r Anne M. Baker	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *19-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 37-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 & 11* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

The response filed November 13, 2000 (Paper No. 10) has been entered. Applicants' election without traverse of Group I, Claims 1-18 and 37-43 in Paper No. 10 is acknowledged. The elected invention is drawn to a method for treating negative symptoms of schizophrenia, a pharmaceutical composition comprising therapeutic cells, and a kit comprising therapeutic cells.

Claims 1-43 are pending in the instant application.

Claims 19-36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 10.

Claims 1-18 and 37-43 are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18, 38, 42, and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for treating negative symptoms of schizophrenia, a pharmaceutical composition comprising therapeutic cells, and a kit comprising therapeutic cells.

The specification fails to provide an enabling disclosure for the method for treating negative symptoms of schizophrenia in a subject because the specification does not adequately teach how to use the

claimed method to produce the intended effect. In Example 1, the specification discloses that Vervet monkeys were administered PCP by intramuscular injection and subsequently were given human RPE cells adhered to crosslinked gelatin microspheres. However, the specification does not disclose what effect these cells had on the negative symptoms provoked by PCP injection. The etiology of schizophrenia is not well understood and treatment of the disease is generally limited to treating specific symptoms (National Institute of Mental Health, Schizophrenia, 1999, pp. 6-7). Although dopamine **antagonists** have been shown to be effective in treating the symptoms of schizophrenia, the effect of dopamine **replenishment** in specific areas of the brain is not known.

The claimed methods encompass methods of *ex vivo* gene therapy, wherein the therapeutic cells are genetically altered so that they produce dopamine or a dopamine precursor, and cell-based therapies, wherein the therapeutic cells naturally produce dopamine or a dopamine precursor. Furthermore, the protective cells and support cells may be genetically engineered cells or unmodified cells, such as glial cells (see pages 9-10 of the specification).

The specification fails to provide an enabling disclosure for the claimed method because the specification teaches that the only use for the method is for therapy, but the specification does not teach how to use the method to produce a therapeutic effect. With regard to the *ex vivo* gene therapy aspects of the claimed methods, the specification fails to teach any method for transferring any gene into a therapeutic cell and expressing that gene at a therapeutic level in the appropriate location in a diseased animal. In U.S. Patent No. 5, 447,948, Seibyl et al. discloses that mesofrontal dopamine deficits may be implicated in the negative symptoms of schizophrenia (Column 1, lines 44-57). Thus, most schizophrenics experience minimal negative symptom improvement or even worsening with standard neuroleptic treatment. The pathophysiology of schizophrenia includes both increased dopamine tone (in mesolimbic dopamine tracts)

and decreased dopamine tone (in mesofrontal dopamine tracts). Seibyl et al. points out that the treatment of schizophrenia with standard neuroleptics results in global reductions of dopamine neuron function in all dopamine tracts and thus may be responsible for the ineffective or deleterious responses of negative schizophrenic symptoms of neuroleptics. Given that dopamine **antagonists** are typically used in the treatment of schizophrenia, the success of the instantly claimed method is critically dependent on **producing dopamine** in a specific location such that the claimed therapeutic effect of reducing the negative symptoms of schizophrenia is achieved. However, for the reasons discussed below, it is not a routine matter to produce dopamine or any other biologically active molecule at the desired level in the desired location using *ex vivo* gene therapy or cell-based therapies. In the instant case, the specific location of dopamine production is critical to successfully producing the desired therapeutic effect, but the specification does not provide adequate guidance for producing the requisite level of dopamine in the appropriate location. The specification fails to provide an enabling disclosure for the use of the claimed method in *ex vivo* gene therapy applications because the specification does not offer adequate guidance in this regard and because methods of gene therapy are not routinely successful. Therefore, the disclosure must teach how to use the claimed method with specific guidance. However, the specification does not provide adequate guidance as to the use of the claimed method to treat a diseased mammal. The specification does not teach the level of gene expression required, the number of transduced cells needed, when or for how long the gene should be expressed, or the frequency of administration of the transfected therapeutic cells (and/or protective cells and support cells) required, for treatment of the negative symptoms of schizophrenia. At the time the application was filed, the art of administering any type of genetic expression vector, including transfected cells, to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH *ad hoc* committee to assess the current status and promise of gene therapy reported in December 1995 that

"clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use the claimed method of *ex vivo* gene therapy and/or cell-based therapy. Thus, absent any showing that the claimed method can be used to produce the intended therapeutic effect, the claims directed to methods for *ex vivo* gene therapy and cell-based therapies are not enabled by the disclosure.

The specification fails to provide an enabling disclosure for the method of cell-based therapy because methods of transplantation of neural tissue or other cells into the CNS are not routinely successful and the specification does not offer adequate guidance to enable one skilled in the art to practice the claimed invention to derive a therapeutic benefit in a diseased animal. The specification teaches that the only use for the claimed method of transplantation is to produce a therapeutic effect but the specification does not adequately teach how to use the claimed method to produce such an effect. Jackowski et al. (1995) details the limitations and unpredictability associated with the transplantation of neural tissue. The specification does not offer any guidance as to how this method could be used therapeutically for the treatment of the negative symptoms of schizophrenia. No working examples demonstrate a therapeutic effect for the claimed method of transplantation. The specification fails to provide any guidance relating to the number of cells to inject, the

site of injection, and the extent of cellular persistence required and attainable in practice, to provide any therapeutic benefit for the treatment of schizophrenia.

With regard to Claim 18, which recites that the positive symptoms of schizophrenia are also alleviated, the specification fails to provide an enabling disclosure for producing this effect. Given the teachings as noted above with regard to the treatment of schizophrenia with dopamine antagonists, the skilled artisan would not expect that the production of dopamine in those regions of the brain which exhibit a dopamine deficit, would alleviate the positive symptoms of schizophrenia, as the positive symptoms are typically treated by inhibiting the action of dopamine. Furthermore, the specification does not provide specific guidance for any protocol that would alleviate the positive symptoms of schizophrenia using a dopamine replenishment strategy.

Given the lack of specific guidance in the instant specification for producing the claimed effect of treating the negative symptoms of schizophrenia, the limited working examples, the unpredictable state of the art with respect to *ex vivo* gene therapy and cell-based therapies, the broad scope of the claims encompassing the use of any cell type as therapeutic, protective, or support cells, one of skill in the art would have been required to engage in undue experimentation to practice the claimed methods and to make compositions as claimed, useful for the treatment of schizophrenia.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 37 is rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,750,103 (Cherksey, 1998).

The claim is directed to a pharmaceutical composition comprising therapeutic cells and protective cells adhered to a support matrix.

Cherksey (1998) discloses therapeutic cells that produce dopamine and which are adhered to a support matrix. Cherksey specifically discloses retinal pigment epithelial (RPE) cells and chromaffin cells adhered to the surface of a support matrix (see Claims 1 and 7). Given that RPE cells are also defined as protective cells within the context of the instantly claimed invention (see page 9, lines 20-23) of the instant specification), the embodiments disclosed by Cherksey satisfy the limitation of including protective cells in the composition as disclosed.

Thus, the claimed composition is disclosed in the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,750,103 (Cherksey, 1998).

The claims are directed to a kit comprising therapeutic cells that produce dopamine and a support matrix, wherein the cells can be adhered to the support matrix.

Cherksey (1998) discloses therapeutic cells that produce dopamine and which are adhered to a support matrix. Cherksey specifically discloses retinal pigment epithelial (RPE) cells and chromaffin cells adhered to the surface of a support matrix (see Claims 1 and 7). Given that RPE cells are also defined as protective cells within the context of the instantly claimed invention (see page 9, lines 20-23) of the instant specification), the embodiments disclosed by Cherksey satisfy the limitation of including protective cells in the composition as disclosed.

It would have been obvious to put the cells and the support matrix in suitable packaging (as recited in Claim 39) or in separate containers (as recited in Claim 40) to produce a kit because, as Cherksey discloses multiple cell types and multiple support matrices suitable for use in the method disclosed by Cherksey, the availability of the cells and the support matrices in separate containers would be desirable so that specific combinations of cell type and support matrix could be conveniently obtained.

Therefore, the claimed compositions would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER